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37. NOTE ON THE SYNTHESIS OF C-TOXIFERIN-I FROM WIELAND-GUMLICH-ALDEHYDE

COMPARISON OF TOXICITY OF SYNTHETIC AND NATURAL CURARE-ALKALOIDS

(Following is the translation of an article by F. Berlage, Karl Bernauer, W. von Philipsborn, P. Waser, H. Schmid and P. Karrer, Chemical Institute of the University of Zurich, published in the German language periodical Helvetica Chimica Acta 42, (1959), pages 394-397. Translation performed by C. L. Lust.)

In the 36th report of this series we reported the synthesis via self condensation of Wieland-Gumlich-aldehyde (V) of Caracurin-V (XII) Alkaloid, which was previously isolated from Strychnos toxifera. The solution was in acetic acid-sodium acetate at 80°. This synthesis will be expanded in subsequent reports. XII can be transformed into N(b)-Dimethylcaracurin-V (XV) with methyl iodide. XV should yield C-toxiferin-I (XIII) in a H ion-catalyzed reaction.

We also mention in that report that if N_b-methyl-Wieland-Gumlich aldehyde (XIV) is heated to 70° in HAC-NaAc a mixture of C-toxiferin-I (XIII) and N_b-dimethylcaracurin-V (XV) results (4). In the meantime we found that the reaction mixture, from which C-toxiferin-I (XIII) can be separated as the chloride in fractional crystellization in 20-25% yield, also contains diacetyl-C-toxiferin I (IR absorbtion at 5.8 μ in KBr). Since some starting material remains this is a four-component-mixture. This could be separated in a long process with paper chromatography.

In either case satisfactory yields should be realized; whether toxiferin-I is made via Wieland-Gumlich-Aldehyde (V) or from the N_b-methyl compound the N_b-dimethylcaracurin-V (XV) compound is an intermediate step.

We devised experiments to find a good method for the rearrangement of N_b-dimethylcaracurin V (XV) to C-toxiferin-I (XIII). It has long been known that the analogous reaction in the tertiary series, namely Caracurin-V (XII) to Caracurin-Va (= Nor-C-toxiferin I) (XI) can be done in dilute mineral acid (5). Yields are very low, because Caracurin-V (XII) is hydrolized to Caracurin-VII (Wieland-Gumlich Aldehyde) (V). Experiments to change N_b-Dimethylcaracurin-V (XV) in a water slightly acidic buffer solution into C-toxiferin-I (XIII) were partially successful (see experimental). However, here also the yields are influenced by hydrolysis. Experiments with water-free acids in organic solvents lead to the goal. Particularly good was HAC-p-Toluensulfonic acid because the toluensulfonates of compounds XV and XIII were soluble in glacial HAC. A solution of HAC 0.02 m and N_b dimethyl-caracurin-v-dichloride (XV) has a yellow-orange color after addition of twice the volume of an 0.08 m HAC solution of p-toluensulfonic acid. The rearrangement of XV to C-toxiferin-I occurs very rapidly in this mixture. After 15 minutes at 20° the product has a UV spectrum of pure C-toxiferin I. Paper chromatographically one sees that the diacetyl derivative of XIII was also formed. After saponifying the mixture for 4 hours with concentrated NH_3 at room temperature the yield of product C-toxiferin-I (XIII) is 75% of theory.

Starting with Nb-methyl-Wieland-Gumlich Aldehyde (XIII) a rational synthesis of C-toxiferin-I (XIII) is as follows:

1.) Selfcondensation of XIV in HAC-NaAc (results in XIII, diacetyl XIII, XV).

2.) Rearrangement of XV present reaction mixture to XIII and diacetyl with p-toluensulfonic acid in HAC.

3.) Saponification of diacetyl XIII.

If this process is done in these three steps, without separating components, and then picrate precipitation used in order to remove starting material (6) and inorganic compounds the yield of XIII is 62% as referred to initial amount of XV.

The easily synthesized alkaloids C-toxiferin I, Nb-dimethylcaracurin-V, C-dihydro toxiferin (1), and dihydro-toxiferin(I*) (2) were tested for toxicity in mice. The corresponding natural alkaloid was used as a comparison (see table). The agreement was very good for the specific tests. Variations between tests (as for C-dihydro XIII) may be attributed to differences in susceptibility of animals (Various shipments were used).

Of note is the observation that XV was much less effective than the isomeric and closely related XIII.

Experimental Part

1.) Nb-Dimethylcaracurin-V (XV). A benzene solution of Caracurin V (XII) is reacted with excess methyl iodide. After two hours at room temperature the liquid is removed. Methyl iodide is removed by, a adsorbing Cl-amberlite IRA 400, changing to chloride. Specific optical rotation is determined (recrystellized 2x MeOH-ether) colorless needles $[\alpha]_D^{22} = +52 \pm 2$ (C = 0,4828, H_2O). One sample of chloride is changed to picrate and recrystallized from acetone-water; yellow needles M point 250°.

$C_{52}H_{50}O_{16}N_{10}$ (1071,0) Calculated C-58.31; H 4.71%; Found C 58.2 H 5.1%

2.) Transforming Nb-Dimethylcaracurin-V (XV) to C-toxiferin -1 (XIL).

a.) pH 4.2 buffer 13.9 mg XV-dichloride in 3 ml 4.2 pH buffer (McIlvaine 1:10) dissolve, and after deaeration in high vacuum heat 24 hours in boiling H_2O bath. Following this precipitate with saturated sodium picrate solution. After two hours remove liquid and wash with H_2O. Picrate can be recrystallized from acetone-water. After drying at 80° in vacuum = 9.44 mg C-toxiferin-1 dipicrate 44.6% yield. Supernatant solutions above contained only XIV (Wieland-Gumlich aldehyde chloromethylate). Varying the pH (3.6, 4.0) and temperature 60° and reaction time did not improve results.

b.) With p-toluensulfonic acid in HAC, 23.2 mg XV dichloride were dissolved in 2 ml HAC and reacted with 1 ml 0.08 m solution of p-toluensulfonic acid in HAC. The yellow-brown mixture is left 15 minutes at room

temperature, then acid is neutralized with soda (colorless!). Evaporate in vacuum. Picrate is precipitated and 2x recrystallized from acetone-water yield = 15.9 mg yellow leafs of XIII-dipicrate (purity checked with paper-chromatography). Mother liquors contained XIII and diacetyl XIII. They are made in chlorides and saponified 4 hours with concentrated NH_3 (10 ml). Evaporation yields a yellow compound which was 7.3 mg pure XIII-dichloride after recrystallization. Total yield XIII 75%.

over

3.) C-toxiferin-I (XIII) from N_b-methyl-Wieland-Gumlich-aldehyde (XIV).

a.) Preliminary experiment:

500 mg XIV chloride and 1 g Na acetate (Anhydrous) aredissolved in 40 ml HAC. After evacuating air, keep tightly closed (sealed) in 70° water bath for 15 hours. Then dry in vacuum. The residue dissolved in water is passed through IRA 400 (cl-) and then again dried in vacuum. This residue is extracted with absolute ethanol. From the extract solution crystallized 177 mg XIII-dichloride after concentrating volume and addition of absolute ether (contaminated by diacetyl XIII dichloride) (Mother liquor 1). Re-crystallization from MeOH-ether = 148 mg XIII dichloride (still some XIII diacetyl cl-) (Mother liquor 2). Recrystallization from MeOH-ether yields 83 mg pure XIII dichloride (Mother liquor 3). The residue of mother liquor 3 (65 mg) is placed in 3 ml concentrated ammonia 4 hours, room temperature. The residue upon recrystallization from MeOH-ether yields 53 mg pure XIII dichloride (Mother liquor 4). The residues from mother liquors 1,2,4 were combined and dissolved in 5 ml HAC; 2.5 ml 0.08 m p-toluensulfonic acid in HAC was added. After 15 minutes at room temperature the p-toluensulfonic acid is neutralized with soda. The mixture is evacuated. From the concentrated water solution of the residue the picrate is precipitated, and with water washing changed into the chloride. This chloride mixture is saponified as above. After evacuation a yellow residue remains. This is recrystallized from Ethanol-methanol and yields 130 mg pure XIII-dichloride. The total yield is then 266 mg XIII dichloride, 55% yield (in terms of starting XIV dichloride.) Purity, etc. checked with IR (2) paper chrom, UV spectrum. Spec. Rotation XIII-dichloride $[\alpha]_d^{22} = -546 \pm 6$ C=0.2959 H_2O). A sample of XIII dichloride picrate, recrystallized M P = 257-260° (decomposes) (10).

$C_{52}H_{50}O_{16}N_{10}$ (1071)

Calculated C 58.31 , H 4.71, N 13.08%
Found C 58.2 , H 4.8, N 12.48%

b.) Main experiment.

500 mg XIV dichloride as in a) selfcondensation. After passing through chloride exchanger the product is dissolved in 10 ml HAC. (NaCl is removed). To this solution is added 5 ml of 0.08 in p-toluensulfonic acid solution. After 15 minutes at room temperature it is neutralised as above. Dried in vacuum. From the concentrated water solution of the residue the picrate is precipitated. Further work up as in a). Yield is 300 mg pure, crystallised XIII dichloride (62% yield).

Summary

A good preparative method is described to produce C-toxiferin-I from Wieland-Gumlich-aldehyde.

1.) Selfcondensation of N_b-methyl-Wieland-Gumlich Aldehyde to C-toxiferin-I, diacetyl C-toxiferin-I, and N_b-dimethylcaracurin-V;

2.) Conversion of N_b-dimethylcaracurin-V in the reaction mixture to C-toxiferin I, and diacetyl C-toxiferin I via toluensulfonic acid and in HAS;

3.) Saponification of diacetyl-C-toxiferin I.

The toxicity of the synthetic alkaloids C-toxiferin I, Nb-dimethyl-caracurin-V, C-dihydro toxiferin, and dihydro toxiferin-I* was tested and compared to the corresponding natural alkaloids. The toxicities of the synthetic and natural compounds were very similar.

Toxicities

Alkaloid		HD	SL	Death[7]
C-Toxiferin-I-dichlorid (XIII)	synthetisch	10	13	22
	natürlich	9	12	23[8])
Caracurin-V-dimethochlorid (XV)		550	600	750
C-Dihydro-toxiferin-dichlorid	synthetisch	40	55	100
	natürlich	45	55	100
Dihydro-toxiferin-dichlorid (I*)		30	30	50
C-Dihydro-toxiferin-dichlorid, ...		29	30	46
(zum Vergleich)				

HD = Head drop doses
SL = doses which caused mice to lie down (gamma;Kg)

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